firmed that B-CLL cells express CD27 at a higher intensity than do normal CD5+ B-cells.[4] CD27 expression on the other entitites was not significantly different from that on the normal B-cell counterpart. The cases analyzed included cases of SLVL. The diagnostic differentiation of SLVL from HCL may be difficult in some cases and even the scoring system proposed by Catovsky can be insufficient.[6] In our series CD27 distinguished HCL (CD27−) from SLVL (CD27+). Although we examined only 5 cases of SLVL, the homogeneous findings reflect evidence from larger series that SLVL tumor cells express CD27 in the periphery.[10]

Our report describes the pattern of CD27 expression on different B-cell neoplasms. Expression occurs in all entities, with the exception of HCL, which regularly lacks surface CD27 protein. Evaluation of CD27 expression may be an additional complementary tool for routine immunophenotypic differential diagnosis among leukemic mature B-cell malignancies.

Francesco Forconi, Donatella Raspadori, Mariapia Lenoci, Francesco Lauria

Sezione di Ematologia, Dipartimento di Medicina Clinica e Scienze Immunologiche, Università di Siena, Italy

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Correspondence: Francesco Forconi, MD, DM, PhD, Sezione di Ematologia, Dipartimento di Medicina Clinica e Scienze Immunologiche, Policlinico Le Scotte, Università di Siena, Italy. Phone: international +39.0577.586798. Fax: international +39.0577.586185. E-mail: forconif@unisi.it

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Chronic Lymphoproliferative Disorders

Delayed response to fludarabine in lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia

We retrospectively reviewed time to response and incidence of delayed responses in 13 patients with lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia (LPL/WM) treated with fludarabine with or without cyclophosphamide. During follow-up post-treatment, seven delayed responses (54%) were observed, improving the initial overall response rate of 61% to a final response rate of 77%.

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Several reports document the efficacy of fludarabine in lymphoplasmacytic lymphoma (LPL) and Waldenström's macroglobulinemia (WM) in both untreated patients[1-2] and in those with relapsed/refractory disease,[2-5] but few have focused on the timing of response. We retrospectively reviewed time to response and incidence of delayed responses in 13 patients with LPL (including 7 with WM) treated with fludarabine with or without cyclophosphamide. The patients' characteristics are summarized in Table 1. Three patients were previously untreated; 10 had relapsed after or were refractory to alkylating agents. Eight patients received single agent fludarabine (25 mg/m^2 intravenously (iv) for 5 days or 40 mg/m^2 orally (p.o.) for 5 days) every 4 weeks for a median of 6 courses (range 4-6). Five patients received fludarabine (25 mg/m^2 i.v. for 3 days or 24 mg/m^2 os for 5 days) with cyclophosphamide (FC) (250 mg/m^2 iv for 3 days or 150 mg/m^2 p.o. for 5 days) every 4 weeks for a median of 8 courses (range 5-9). The number of courses was determined by clinical and laboratory evidence of what was thought to be the maximal achievable response. Conventional criteria for complete response (CR) and partial response (PR) were used.[6] We also defined serological CR (sCR) as the absence of detectable serum and urine paraprotein by immunofixation, resolution of organomegaly, but with residual bone marrow (BM) disease (<50%). Patients not fulfilling these criteria were non-responders (NR). Any subsequent improvement in response during treatment-free follow-up constituted a delayed response.

The overall response rate assessed 1 month after completing therapy was 61% (23% sCR; 38% PR). Seven delayed responses (54%) were observed: 2/7 NR achieved PR two and seven months from the end of therapy and 2/5 with a PR reached sCR two and five months after completion of fludarabine (Table 1). In addition, 3 patients with a PR experienced further reduction in their paraprotein level, although insufficient to attain sCR: one patient (#12) achieved an 84% reduction 25 months after stopping FC and two others (#13, #7) 89% and 90% reduction 9 and 5 months after stopping therapy, respectively (Figure 1). The final response rate improved to 77% (10/13), including all 5 patients treated with FC and 5 of the 8 treated with fludarabine. All 3 previously untreated patients and 7 of 10 previously treated patients responded. The sCR rate was 38%; BM histology showed nodular PR (#4, #9, #10) or PR (#11) in 4 and CR (#8) in one. Thus, the final CR rate was 8%. Nodal disease resolved during treatment in all responders regardless of the tim-

Table 1. Patients' characteristics and response to fludarabine (F) alone or plus cyclophosphamide (FC).

						Clinical characteristics before F or FC				Response to treatment			
Case#	Sex/Age (yrs.)	Diagnosis	Previous treatment	Response to previous treatment	Organo megaly	Other	Paraprotein (g/L) and class	B-J	β2m (mg/L)	Therapy (#number of courses)	End of therapy	Maximal response (months after stopping)	BM response	Follow-up (months from the start of F or FC)
1	F/70	LPL	CHL; CY	Refractory relapse postPR	–		18 (IgMκ)	N/A	N/A	F (# 5)	NR	NR	None	Dead (+14m)
2	M/68	WM	p-e; CY	Refractory	N/A	Neuropathy	11 (IgMκ)	Neg	2.7	F (# 4)	NR	NR	–	Lost to f-up (+24m)
3	M/31	WM	CHL+PDN	Refractory	A (neck)	Amyloidosis Nephrotic syndrome	45 (IgMκ)	Pos	N/A	F (# 6)	NR	NR	None	Lost to f-up (+16m)
4	F/46	LPL	CHL; p-e	Minor response	–		3 (IgMκ)	Neg	1.5	F (# 6)	PR	sCR (2 m)	NodPR	Relapsed (+36m) and alive (+73m)
5	M/78	WM	CHL + RT	Relapse postPR	A (neck)		38 (IgMκ)	Pos	4.5	F (# 5)	NR	PR (2 m)	N/A	Dead from ITP in PR (+9m)
6	M/58	WM	CHL	Refractory	–		42 (IgMλ)	Pos	1.8	F (# 6)	NR	PR (7 m)	N/A	Alive in PR (+123m)
7	M/57	WM	Cy; CHL	Relapse post PR	–		29 (IgMκ)	Neg	1.0	F (# 6)	PR	PR (5 m)	CR	Alive in PR (+23m)
8	F/53	LPL	CHL; p-e	Refractory	–	Cryoglobulinemia Ischemic skin lesions	8 (IgMκ)	N/A	2.4	F (# 6)	PR	CR (5 m)	CR	Lost to f-up in CR (+11m)
9	F/56	LPL	CHL (1#); PDN	Minor response	A (axilla retroperitoneum, 2 cm)		5 (IgMκ)	Pos	3.5	FC (# 8)	sCR	sCR	NodPR sCR (+36m)	Alive in
10	F/63	LPL	–		A (axillae, widespread retroperitoneum, mesentery) S (12 cm)		11 (IgMκ)	Neg	7.8	FC (# 5)	sCR	sCR	NodPR	Alive in sCR (+39m)
11	M/66	LPL	CHL+PDN	Minor response	–		5 (IgMκ)	Pos	3.6	FC (# 6)	sCR	sCR	PR	DLBCL (+8m) Alive in CR (+37m)
12	M/43	WM	–	–	A (neck,2cm) S (5 cm)		37 (IgMκ)	Pos	4.1	FC (# 9)	PR	PR (25 m)	PR	Relapsed (+68m) and alive (+81m)
13	M/55	WM	–	–	–		37 (IgMκ)	Pos	<0.5	FC (# 8)	PR	PR (9 m)	PR	Alive in PR (+18m)

N/A: not available; A: adenopathy; S: splenomegaly; B-J: Bence-Jones proteinuria; β² m: β² microglobulin; CHL: chlorambucil; CY: cyclophosphamide; p-e: plasma-exchange; PDN: prednisone; RT: radiotherapy; NR: non-responder; PR: partial response; CR: complete response; sCR: serological complete response; BM: bone marrow; NodPR: nodular PR; ITP: immune thrombocytopenia; DLBCL: diffuse large B-cell lymphoma.

ing of paraprotein response. The median halving-time of serum paraprotein for the 10 responders was 5 months and the median time for maximum paraprotein reduction was 8 months (range 3-35) from the start of therapy. The 7 late responders achieved maximum serum paraprotein reduction 5 months (range 2-25) after stopping chemotherapy. Delayed responses were seen in all patients responding to fludarabine (5/5) and in 2/5 responders to FC.

In published reports, most responses occur 3-6 months after the start of fludarabine with a median halving time of serum paraprotein ranging from 1.5 to 5.4 months. A SWOG study on 118 patients with WM treated with fludarabine documented delayed responses (6 months from the beginning of therapy) in 17%.[2] Another report on 6 patients quoted a median of 17 months (range 2.2-35.6) for maximum paraprotein reduction after completion of fludarabine.[7] Our analysis further supports this phenomenon in a larger proportion of patients (54%). In fact, more than two-thirds of responders had an improvement in the quality of their response after completing treatment, with 2 initial NR subsequently achieving PR. No association with the number of chemotherapy courses was observed.

There are scanty data on the use of FC in patients with LPL/WM. A report[8] on 11 patients with WM showed 55% PR, but no CR; the median time to response was 4 months. In our series, FC induced responses in all 5 patients treated (3 sCR and 2 PR), 3 of whom were previously untreated. In conclusion, we suggest that a peri-

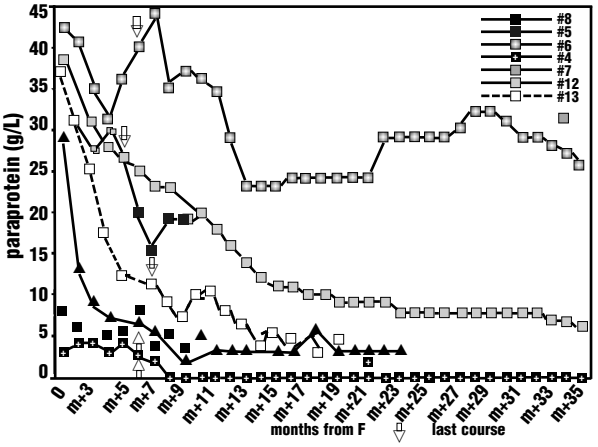

Figure 1. Levels of serum paraprotein during and after treatment with fludarabine or FC in the 7 patients with delayed response. Arrows indicate the last course of treatment.

od of at least 12 months from the end of therapy is required to determine chemosensitivity and maximum response to fludarabine or FC in LPL/WM. Response to therapy should be assessed at disease nadir to avoid missing delayed responses, as recommended by the Second International Workshop on WM.[6] However, neither response to fludarabine nor speed of response is a known predictor for progression-free survival and/or overall survival.[9]

Although treatment with nucleoside analogs in LPL/WM has been associated with a shorter time to response than treatment with chlorambucil, the occurrence of delayed responses, also described after fludarabine, cladribine and rituximab,[10] suggests that the biology of LPL/WM cells may be responsible for this phenomenon regardless of the type of chemotherapy given.

Ilaria Del Giudice, Estella Matutes, Nnenna Osuji, Nilima Parry-Jones, John Swansbury, Daniel Catovsky

Department of Hemato-Oncology, The Royal Marsden Hospital and Institute of Cancer Research, London, UK

Key words: fludarabine, lymphoplasmacytic lymphoma, Waldenström's macroglobulinemia, delayed response.

Correspondence: Ilaria Del Giudice, MD, Department of Haemato-Oncology, Royal Marsden Hospital, 203 Fulham Road, SW3 6JJ, London, UK. Phone: international +44.0207.8082878. Fax: international +44.0207.3516420. E-mail: idelgiu@freemail.it; ilaria.del-giudice@icr.ac.uk

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Chronic Lymphoproliferative Disorders

Direct medical costs of mycosis fungoides in specialized Italian hospital departments

The objective was to analyze direct medical costs of managing mycosis fungoides (MF). We conducted a retrospective observational study in five Italian specialized departments. The 58 patients enrolled had a confirmed diagnosis of MF stage IIB or worse in 1999. The mean cost per patient was € 9,231.40.

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Mycosis fungoides (MF) is an epidermotropic cutaneous T-cell lymphoma (CTCL) causing proliferation of small or medium-sized neoplastic T lymphocytes with cerebriform nuclei.[1] The estimated annual incidence rate of MF is 0.3 per 100,000.[2-5] The treatment of CTCL varies according to the disease stage and the patient's age. Unfortunately, few patients achieve durable complete responses and cure of advanced disease is uncommon. To our knowledge, no article on the costs of CTCL has been published so far. This study is a first attempt to analyze resource utilization and direct medical costs of MF. A secondary aim of the study was to assess differences for clinically defined stages of disease.

We conducted a retrospective observational study in five departments specialized in the management of CTCL. Patients eligible for the study had a confirmed diagnosis of MF stage IIB or worse in 1999, and were still alive in March 2002. The time horizon of the study was two years (2000-2001). Data on patients' utilization of resources were extracted from medical charts and collected using a pre-designed questionnaire. Direct medical costs were estimated from the Italian National Health Service (INHS) perspective. Costs included outpatient and inpatient services delivered in the participating centers. Costs of incidental complications treated outside the participating centers